FDA Introductory Remarks

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety and Risk Management Advisory Committee Meeting

Rigoberto Roca, MD
Division Director (Acting), Division of Anesthesiology, Addiction Medicine and Pain Medicine
Office of New Drugs
Center for Drug Evaluation and Research

Discussion Point #1

Clinical practice guidelines state that opioids should not be used as the initial therapy for patients with chronic low back pain and should only be used when patients have not responded adequately to non-opioid and non-pharmacologic therapies. Discuss whether the Applicant enrolled an appropriate patient population.

Discussion Point #2

The Applicant conducted one pivotal efficacy study. Given that oxycodegol is a full mu-opioid receptor agonist, discuss if the data from the one efficacy study are substantial enough to support an indication in patients with chronic low back pain who have not responded adequately to non-opioid and non-pharmacologic therapies.

Discussion Point #3

Based on the available safety data, discuss any concerns you may have about the safety profile of oxycodegol, including whether there is evidence for potential hepatic toxicity. Discuss any recommendations you have for patient management regarding the liver safety findings. Given that patients may use oxycodegol at doses higher than those for which adequate safety data are available, discuss whether any additional data are needed to further inform the safety profile of oxycodegol.

Discussion Point #4

Considering the data that have been provided that address the abuse potential of oxycodegol, please discuss any concerns you have with the evaluation of its relative abuse liability and the potential impact of the abuse liability of this product on public health.

Voting Question

Do you recommend approval of oxycodegol?

A. Yes, for the proposed indication of management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

B. Yes, for a general extended-release/long-acting opioid analgesic chronic pain indication.

C. No

Please discuss the rationale of your vote. If you voted A or B, please specify whether any post-approval studies should be required. If you voted C, please discuss what additional data are needed.


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Regulatory and Clinical Context for the Evaluation of Oxycodegol

Joshua Lloyd, MD

Clinical Team Leader

Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

January 14, 2020

Impact and Management of Chronic Pain

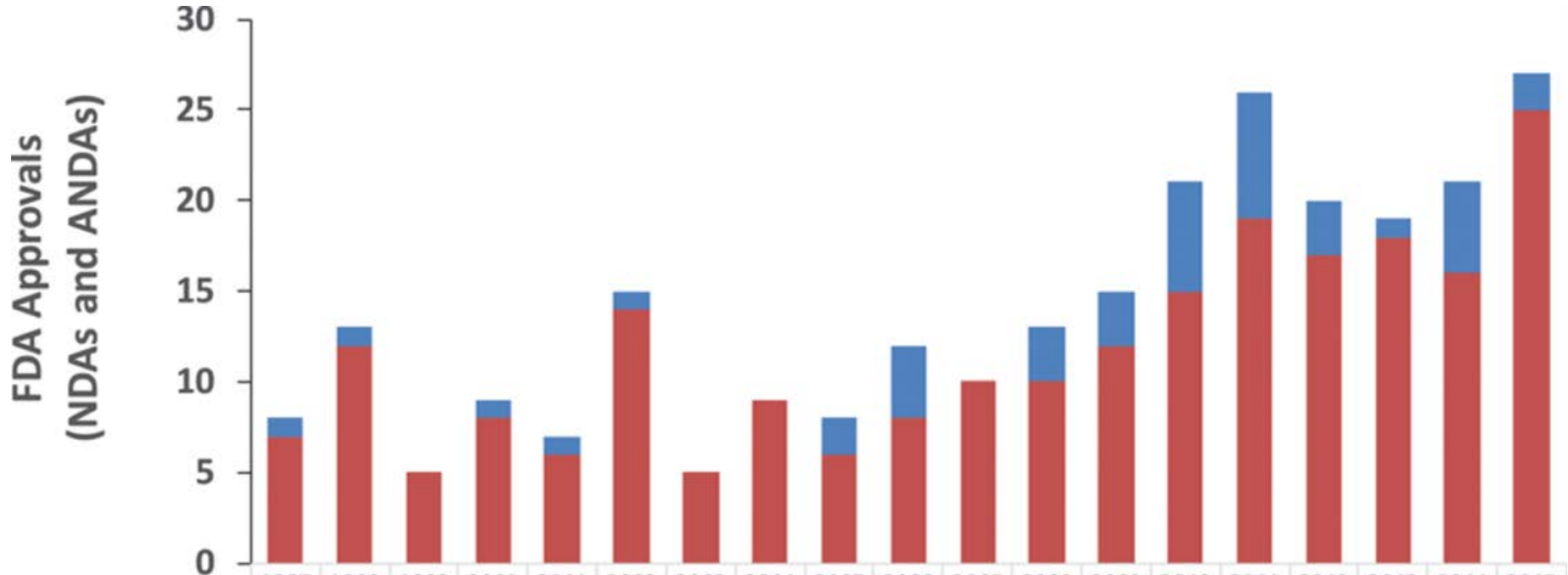
- Chronic pain
  - Serious condition
  - Affects millions of Americans
  - Can have devastating consequences
- Patient management
  - Nonpharmacologic therapy
  - Pharmacologic therapy
    - Opioid therapy
      - For when other treatments are inadequate
      - In patients for whom potential benefits outweigh risks

Opioid Analgesics: A Double-Edged Sword

- Opioids provide analgesia and play a role in pain management
  - Currently approved indications reflect a population for which other analgesics are inadequate
- Opioids are associated with significant safety concerns
  - Public health crisis of misuse, abuse, addiction, overdose, and death
    - Over-prescription has been a major driver in fueling this crisis

Increased numbers of opioid approvals, mostly represented by generics…

Number of U.S. Food and Drug Administration (FDA) approvals of new drug applications (NDAs) and abbreviated new drug applications (ANDAs) for opioid analgesic products by year of approval from 1997 through 2015.



	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
NDA approvals	1	1	0	1	1	1	0	0	2	4	0	3	3	6	7	3	1	5	2
ANDA approvals	7	12	5	8	6	14	5	9	6	8	10	10	12	15	19	17	18	16	25

From: New Opioid Analgesic Approvals and Outpatient Utilization of Opioid Analgesics in the United States, 1997 through 2015. Anesthes. 2018;128(5):953-966.

Opioids in Clinical Practice

- No ceiling effect for analgesia
  - No maximum dose for most opioids
    - The higher the dose, the greater the analgesic effect
    - …and the greater the risk for serious adverse events
- Serious adverse events can occur at any dose
  - Misuse, abuse, and addiction not limited to a particular dose range

Oxycodegol was developed to slow CNS penetration of this novel full mu-opioid receptor agonist

- Oxycodegol binds to the mu-opioid receptor
  - Binding mediates analgesic and undesirable central nervous system (CNS) effects
    - Similar to other full mu-opioid receptor agonists
    - Effects are the sum of oxycodegol and its pharmacologically-active metabolites
- Oxycodegol is PEGylated oxycodol
  - Physicochemical properties are inherent to the molecule
  - Not formulated with any excipients to impart abuse-deterrent characteristics

Regulatory Considerations Regarding the Indication

- Two adequate and well-controlled studies would be needed to support analgesic efficacy
  - Two studies in one population to support indication in that population
  - Two studies in two different chronic pain populations to support the broader ER/LA opioid analgesic indication (i.e., chronic pain)
- Applicant proposed submitting one efficacy study
  - Given oxycodegol is a full mu-opioid receptor agonist
- Issue discussed internally at a Medical Policy Council meeting

The Interface of Clinical Trials and Clinical Practice

- Chronic pain management involves a multidisciplinary approach
  - Analgesic clinical trials do not necessarily inform how an analgesic fits into patient-tailored approaches
- Analgesic clinical trials are intended to demonstrate an analgesic effect
- Novel analgesics
  - Typically require replicated evidence of an effect
    - At least two positive adequate and well-controlled studies
- Oxycodegol application
  - Controlled efficacy data from a single clinical trial
    - Chronic low back pain population
  - Data to demonstrate that oxycodegol is a full mu-opioid receptor agonist

Clinical Considerations: Existing Safety and Efficacy Data

- Efficacy
  - Efficacy data suggest typical dose range may extend higher than studied
  - Applicability of efficacy data to an appropriately selected patient population
    - Applicant was advised to define a patient population for which administration of an opioid analgesic is an appropriate next step in pain management for chronic low back pain
- Safety
  - Maximum labeled dose based on what the safety data support
  - Implications on oxycodegol of opioid analgesics being titrated to effect in clinical practice

Further Considerations

- Oxycodegol was developed to avoid the serious adverse effects associated with opioids, particularly adverse effects related to abuse liability
  - Applicant maintains that oxycodegol has a lower abuse potential than other opioids, particularly in the therapeutic dose range
    - Only viewing abuse liability through lens of therapeutic dose range is arbitrary and flawed
  - FDA review notes that oxycodegol has a high potential for abuse similar to other Schedule II opioids
    - Whether it is more or less liked compared to other opioids with high abuse potential, such as oxycodone, remains to be seen
- Conflicting paradigm
  - Unclear how oxycodegol could exert its analgesic effect through the mu-opioid receptor and only require one efficacy study
    - While at the same time its different enough from other mu-opioid receptor agonists that it does not carry the same abuse liability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Drug Use, Abuse, and Overdose Involving Opioid Analgesics

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

January 14, 2020

Cynthia Kornegay, PhD
Division of Epidemiology II
Office of Pharmacovigilance and Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Assessing the Benefits and Risks of Prescription Opioid Analgesic Products

- Draft Guidance – "Opioid Analgesic Drugs: Considerations for Benefit-Risk Assessment Framework: Guidance for Industry" (FDA, 2019)

  – "FDA also considers the broader public health effect of opioid analgesic drugs; this involves consideration of the risks related to misuse, abuse, opioid use disorder, accidental exposure, and overdose, for both patients and others."

Objective

To inform public health risk/benefit assessment by:

1. Depicting patterns in prescription opioid analgesic utilization and the relative prescribing of extended-release (ER) oxycodone products and other prescription opioid analgesics
2. Presenting epidemiologic data on misuse, abuse, and overdose involving oxycodone products and other opioids
    - No regulatory history available to assess postmarket oxycodegol abuse; closest currently marketed analog is oxycodone

Opioid Analgesic Drug Utilization

ER/LA Opioid Analgesic Utilization

Depicting utilization patterns of opioid analgesic products and frequency of ER oxycodone prescribing in the United States

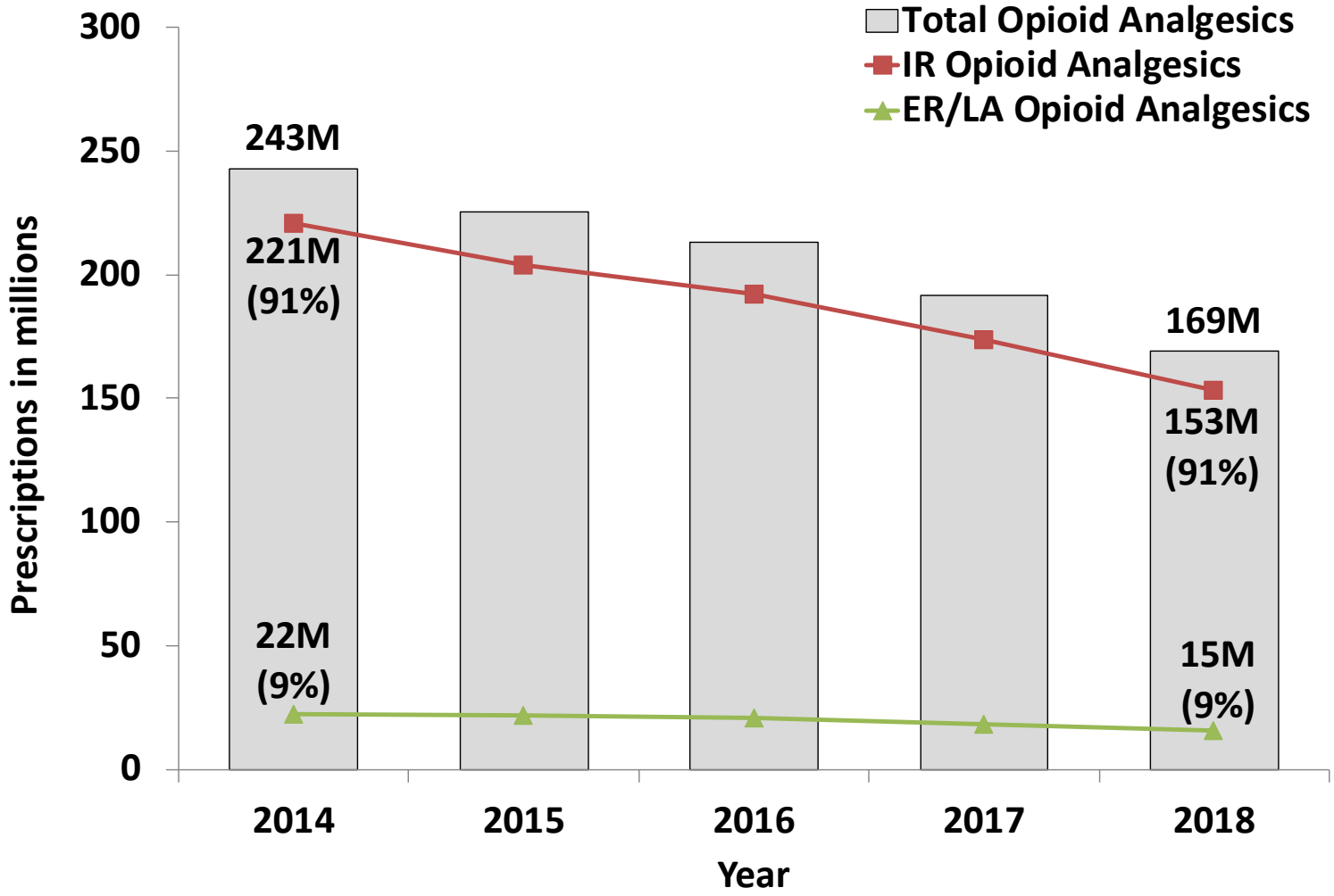
- How has ER/LA opioid analgesic prescribing changed over time?
- How frequently is ER oxycodone dispensed compared to other ER opioid analgesics?
- What diagnoses are associated with ER oxycodone prescribing?

ER: extended release, ER/LA: extended release/long-acting

Outpatient Prescription Dispensing Data Resource Description

- Symphony Health PHAST™ Prescription Monthly database
- Measures dispensed prescription claims from a robust sample of U.S. retail pharmacies
- Data are projected to provide national estimates of utilization

Total Opioid Analgesic Prescriptions Have Decreased Over Time



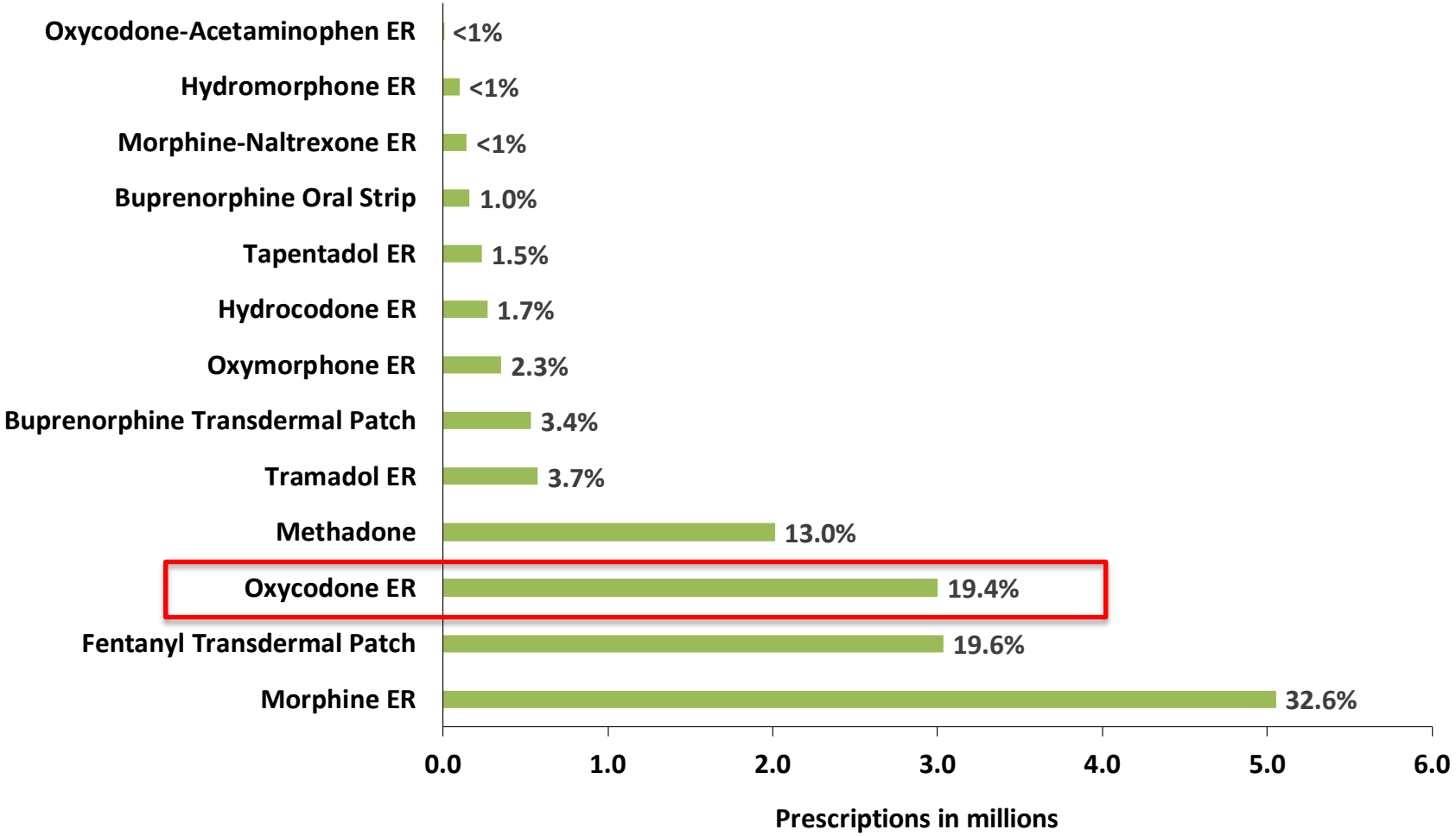
Estimated number of opioid analgesic prescriptions dispensed from U.S. retail pharmacies, 2014-2018

IR: immediate release opioids, ER/LA: extended release/long-acting opioids

Our analysis excluded: 1) opioid analgesics with injectable, topical, and suppository formulations, 2) opioid-containing Medication-Assisted Therapy (MAT) products (e.g. buprenorphine and methadone), 3) opioid-containing cough/cold products, and 4) migraine products containing an opioid, aspirin, butalbital, and/or caffeine.

Source: Symphony Health PHAST™ Prescription Monthly. 2014-2018. Data extracted June 2019.

Oxycodone ER (extended-release) one of the most frequently dispensed ER/LA opioid analgesic products



Estimated number of prescriptions dispensed for opioid analgesic extended-release/long-acting products from U.S. retail pharmacies, 2018

ER/LA: extended release/long-acting opioids

Our analysis excluded: 1) opioid analgesics with injectable, topical, and suppository formulations, 2) opioid-containing Medication-Assisted Therapy (MAT) products (e.g. buprenorphine and methadone), 3) opioid-containing cough/cold products, and 4) migraine products containing an opioid, aspirin, butalbital, and/or caffeine.

Source: Symphony Health PHAST™ Prescription Monthly 2018. Data extracted June 2019.

U.S. Office-Based Physician Survey Data

- Syneos Health Research & Insights LLC, Treatment Answers with Pain Panel database
- Monthly surveys of 3,200 office-based physicians
- Data are nationally projected to reflect national prescribing patterns
- Data provide insight into prescriber intent

Top Diagnoses – ER/LA Opioid Analgesic Products

- Diseases of the musculoskeletal system and connective tissue (M00-M99) such as low back pain: 63% of drug use mentions
- Diseases of the nervous system (G00-G99) such as chronic pain syndrome: 14% of drug use mentions
- Neoplasms (C00-D49): 9% of drug use mentions

ER/LA: extended-release/long-acting
Source: Syneos Health Research & Insights LLC., TreatmentAnswers™ 2018. Data extracted June 2019.

Database Limitations

- Dispensed prescription data
  - No linkage between a dispensed prescription and a diagnosis
  - No medical charts available for validation
  - Dispensing trends may not apply to non-retail or mail-order/specialty settings

- Office-based physician survey data
  - May not capture diagnosis data from subspecialty prescribers in inpatient or clinic settings, such as oncology clinics
  - Dentists are not included in the sample
  - A diagnosis mention does not necessarily result in a prescription being generated

Epidemiologic Overview

Epidemiologic data

Present epidemiologic data on the misuse and abuse of oxycodone products and other opioids to inform public health risk/benefit assessment of oxycodegol

- What is the current scale of misuse/abuse of prescription opioids?
- Which are the most frequently abused opioids?
- What are common routes of abuse for opioids?
- What is the magnitude of morbidity and mortality associated with oxycodone-containing products and other opioids?

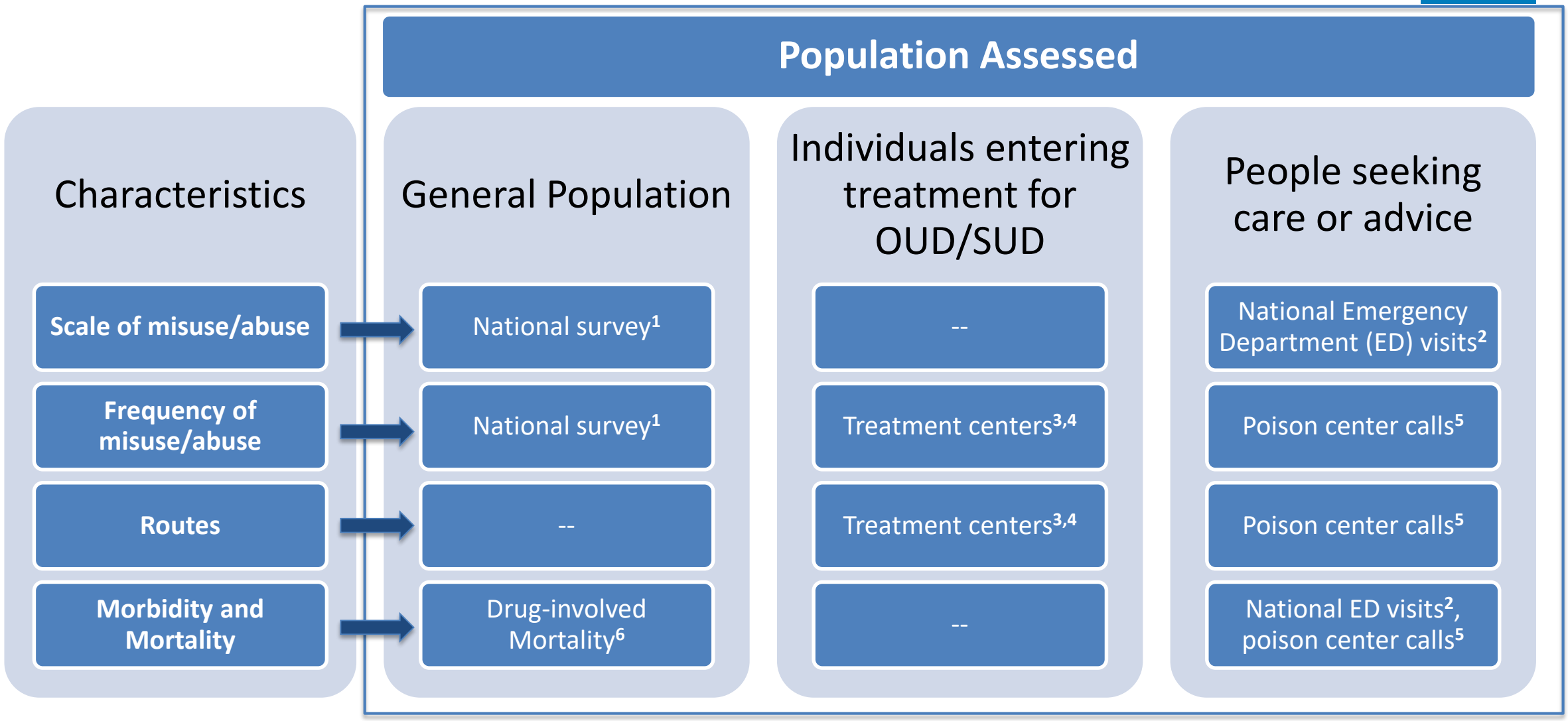
Definitions of Misuse/Abuse

- **Misuse:** the intentional therapeutic use of a drug product in an inappropriate way and specifically excludes the definition of abuse

- **Abuse:** the intentional, non-therapeutic use of a drug product or substance, even once, to achieve a desirable psychological or physiological effect

Food and Drug Administration [Internet]. "Abuse-Deterrent Opioids—Evaluation and Labeling: Guidance for Industry" [updated 2015 Apr; cited 2018 May 10.] Available from: https://www.fda.gov/downloads/Drugs/Guidances/UCM334743.pdf.

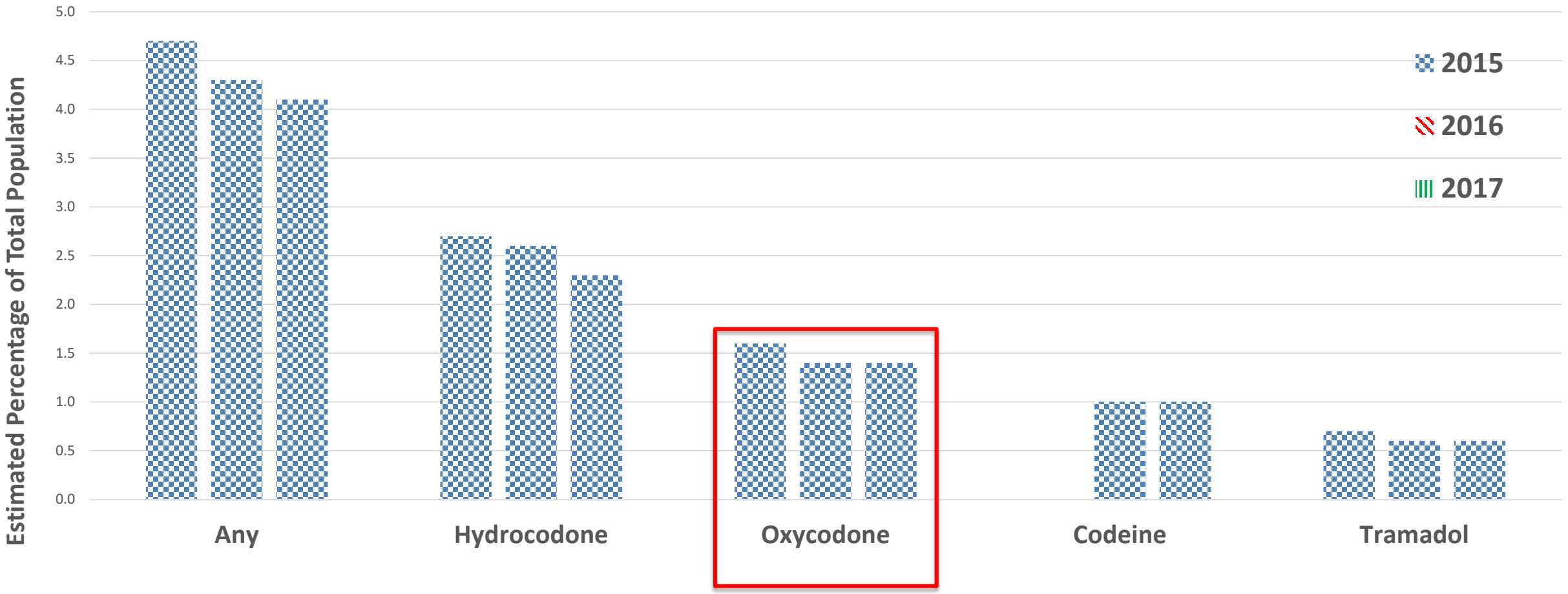
Epidemiologic Data on Misuse and Abuse: A Mosaic Approach



OUD, opioid use disorder; SUD, substance use disorder; **Sources**: 1) National Survey on Drug Use and Health (NSDUH), 2015-2017; 2) National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance (NEISS-CADES) 2016-2017; 3) National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO™) Addiction Severity Index-Multimedia Version® (ASI-MV®), 2016-2017; 4) Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS) System Treatment Center Program (TCP), 2013-2017; 5) the National Poison Data System (NPDS) 2012-2017; 6) Drug-involved Mortality (DIM), 2011-2016

Scale of Misuse/Abuse

Oxycodone continues to be one of the most widely misused opioid analgesics, NSDUH 2015-17



Source: National Survey on Drug Use and Health (NSDUH), 2015-17;
Includes individuals meeting FDA's definition of both misuse and abuse

Decrease in Abuse Exposure Calls for Oxycodone and Comparators, ages ≥ 12 years, AAPCC NPDS 2012-17

Opioid	Abuse Calls in 2012	Abuse Calls in 2017
Oxycodone	2344	1762
Hydrocodone	2336	954
Morphine	542	270
Heroin	2528	6018

- Decrease in calls involving oxycodone, hydrocodone, and morphine
- Increase in heroin-involved calls

Source: American Association of Poison Control Centers (AAPCC), National Poison Data System (NPDS), 2012-17

Relative Frequency of Abuse

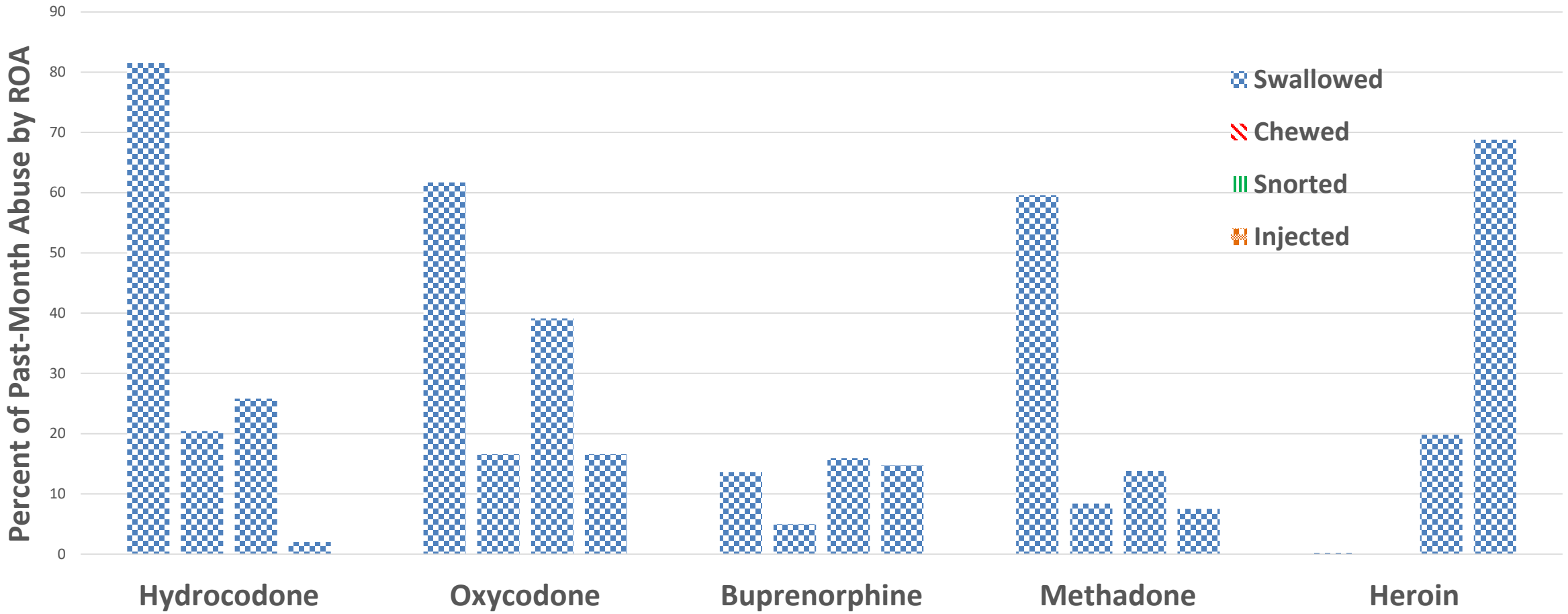
Oxycodone was one of the most common products abused in the past month in persons being assessed for or entering substance abuse treatment

- RADARS TCP: Oxycodone endorsed by 31.7% of individuals entering treatment for opioid use disorder
  - Hydrocodone 24.5%, Buprenorphine 17.9%, Methadone 14.2%

- NAVIPPRO™: Oxycodone endorsed by 9.8% of every 100 individuals being assessed for or entering treatment for substance abuse disorder
  - Buprenorphine 13.0%, Hydrocodone 10.0%, Methadone 5.6%

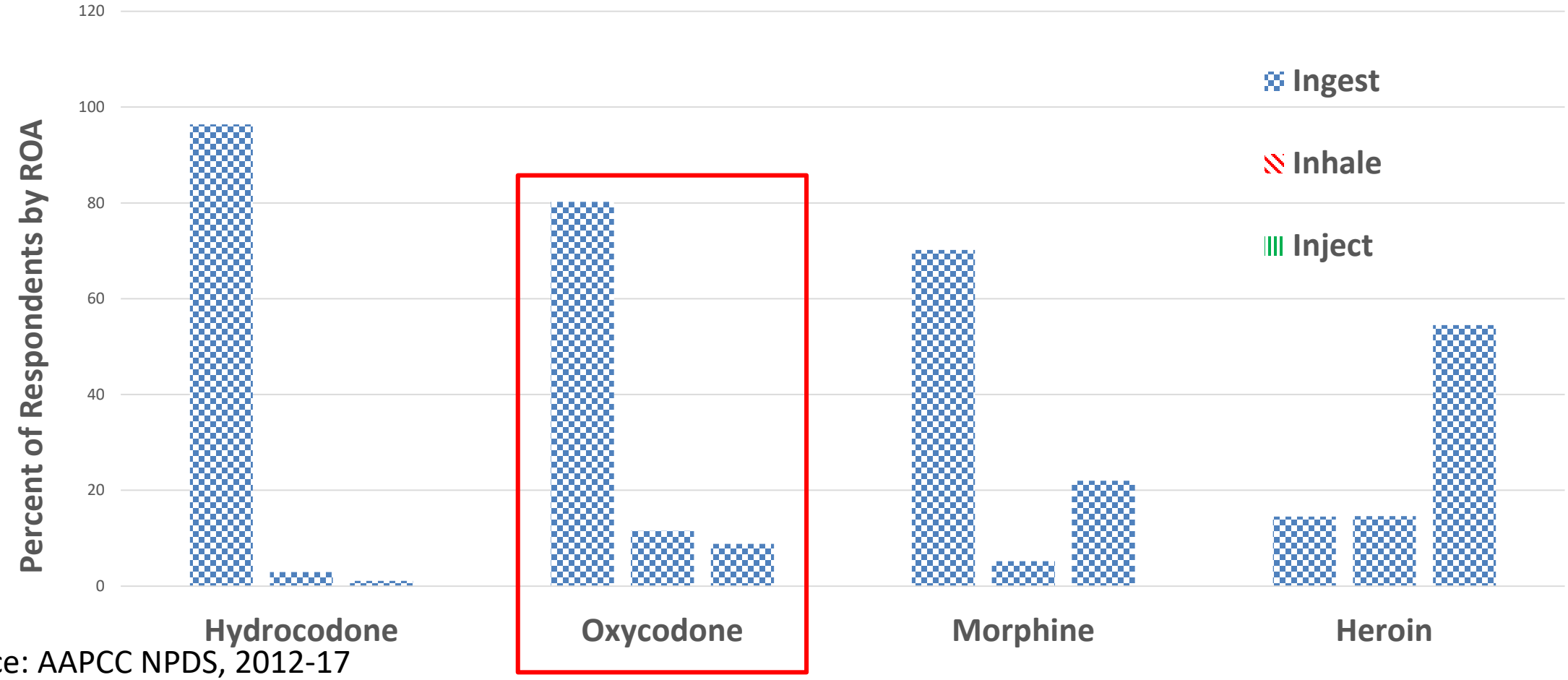
Routes of Abuse

Swallowing/snorting most common abuse routes for oxycodone in individuals being assessed for SUD, NAVIPPRO™ 2016-17



Four most commonly misused opioid analgesic ingredients
Source: NAVIPPRO™, 2016-17 SUD: substance use disorder

Approximately 80% of oxycodone abuse is via ingestion in people seeking treatment or advice, AAPCC NPDS 2012-17



Source: AAPCC NPDS, 2012-17

Morbidity and Mortality

An estimated 35% - 40% of U.S. ED visits for non-medical prescription opioid use involve oxycodone-containing products

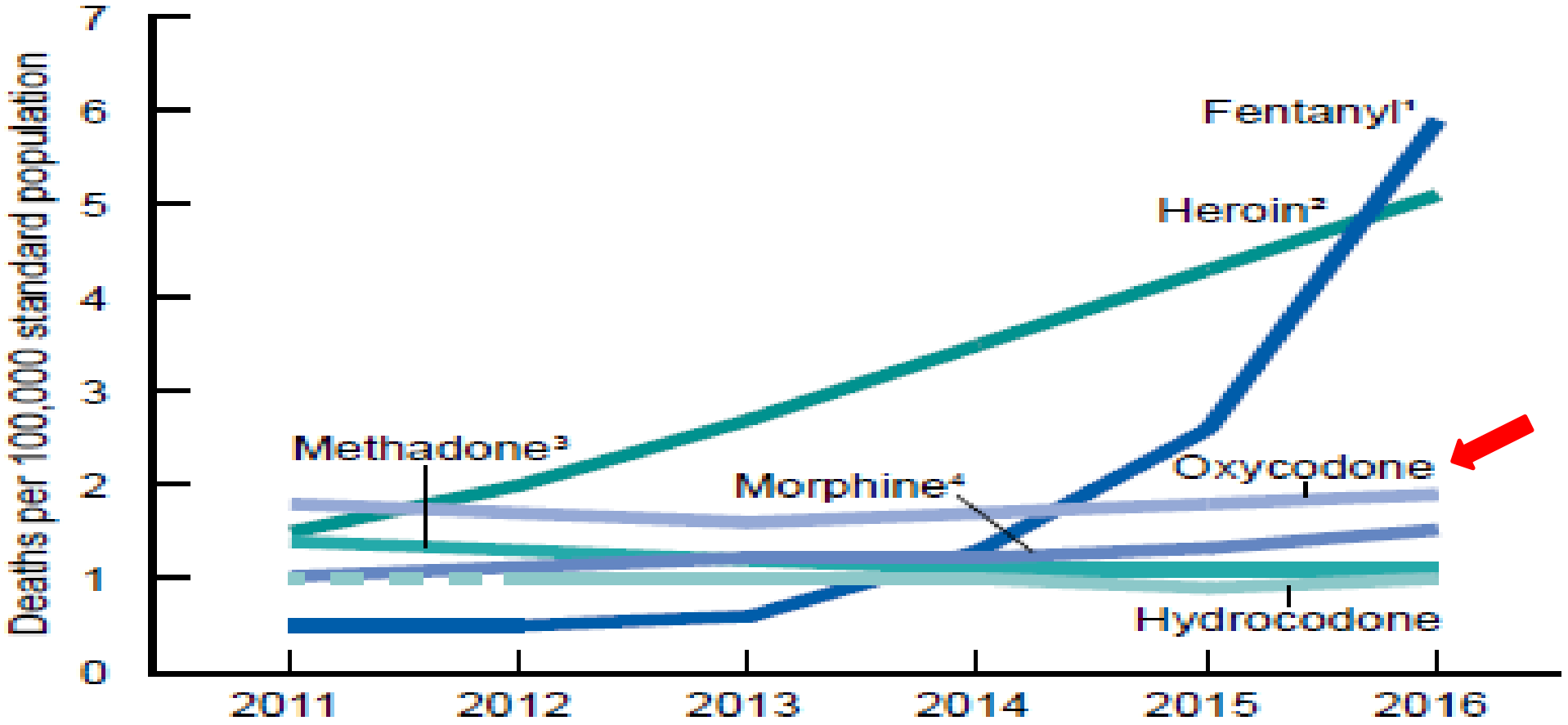
Opioid Analgesic Product	No.	Annual Estimate % of Total Estimate (95% CI)
Non-medical Prescription Opioid Use[a] (Total Annual Estimate = 127,177 ED Visits)		
Oxycodone-containing Product	49,609	39.0 (32.7 - 45.3)
Hydrocodone-containing Product	14,901	11.7 6.1 - 17.3)
Morphine-containing Product	7,814	6.1 (4.0 - 8.3)
Therapeutic Prescription Opioid Use[b] (Total Annual Estimate = 103,786 ED Visits)		
Oxycodone-containing Product	36,997	35.6 (29.3 - 42.0)
Hydrocodone-containing Product	22,647	21.8 (15.7 - 27.9)
Morphine-containing Product	8,175	7.9 (6.2 - 9.5)
Prescription Opioid Self-harm (Total Annual Estimate = 36,057 ED Visits)		
Oxycodone-containing Product	13,707	38.0 (30.7 - 45.3)
Hydrocodone-containing Product	9,478	26.3 19.8 - 32.8)
Morphine-containing Product	2,102	5.8 (4.3 - 7.4)

Source: Data provided by the CDC Division of Healthcare Quality Promotion, ED: emergency department

[a]Includes pharmaceutical abuse, therapeutic misuse (use other than as directed by a clinician), and opioid overdoses without indication of intent.

[b]Includes adverse events from therapeutic use (e.g., adverse effects, allergic reactions, medication errors, and unsupervised ingestions by children).

Age-adjusted overdose death rates for oxycodone remained steady, NVSS-M 2011-16



Age-adjusted rates for drug overdose deaths involving selected opioids,2011-16

Source: Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14.

Summary: Misuse/Abuse

- Scale of Misuse/Abuse
  - In 2017, an estimated 1.4% of the U.S. population aged 12 or older (3.7 million individuals) misused or abused an oxycodone product
  - The number of oxycodone abuse-related calls to AAPCC NPDS decreased from 2344 in 2012 to 1762 in 2017
    - Calls for other prescription opioids also decreased; heroin-related calls increased
- Relative Frequency of Abuse
  - RADARS TCP: Oxycodone was the most common prescription opioid analgesic abused in the past 30 days in a population of individuals entering treatment for opioid use disorder, followed by hydrocodone
    - Heroin was endorsed by more individuals than oxycodone and hydrocodone combined

Summary: Misuse/Abuse (cont.)

- Relative Frequency of Abuse
  - NAVIPPRO™: Buprenorphine was most commonly abused prescription opioid analgesic product, followed by hydrocodone, oxycodone, and heroin
  - In both RADARS TCP and NAVIPPRO™, the number of individuals abusing oxycodone and prescription opioid comparators decreased; the numbers for heroin increased

Summary: Misuse/Abuse (cont.)

- Routes of Abuse
  - Oral (swallowing) was the most common oxycodone abuse route endorsed in AAPCC NPDS and NAVIPPRO™
  - RADARS TCP only tracked non-oral routes before 2018; snorting was the most common route endorsed for oxycodone
- Morbidity/Mortality
  - Oxycodone-containing products were involved in between 35 – 40% of ED visits related to non-medical prescription opioid use, therapeutic use, or self-harm
  - Age-adjusted fatal overdose rates for deaths involving oxycodone were 1.9 per 100,000 in 2016; remained steady during time period examined

ED: emergency department

Key Data Source Limitations

- NSDUH
  - Survey biases: recall, response, social desirability
- NPDS
  - Under-capture of exposures, particularly overdoses resulting in out-of-hospital death[1]
  - Proportion of cases captured may vary over time and by substance
- RADARS TCP/NAVIPPRO™
  - Findings from the included treatment centers may not be broadly generalizable or nationally representative of all patients entering treatment for opioid use disorder;
  - Product misclassification may occur (self-report)

[1]Mallama et al, PDS 2019. Available at https://www.ncbi.nlm.nih.gov/pubmed/31402548

Key Data Source Limitations (cont.)

- NEISS-CADES
  - Does not include cases that result in death before or during ED evaluation
  - Potential for misclassification of products (e.g., oxycodone single ingredient vs. oxycodone combination)
- NVSS-M/DIM
  - Reliance on literal text of death certificate likely to miss proportion of opioid-related deaths that do not contain an ingredient or product in the literal text
  - Death certificate documentation of specific drugs has changes over time, which will also be reflected in trends

ED: emergency department

Conclusions

- Oxycodone and hydrocodone remain the most commonly misused and abused prescription opioids in the general population

- Although heroin is more commonly abused in people entering treatment for opioid use disorder, overall, oxycodone misuse and abuse remains a significant public health burden in terms of morbidity and mortality

Abuse Potential of Oxycodegol

James M. Tolliver, PhD
Shalini Bansil, MD
Controlled Substance Staff (CSS)
Office of the Center Director (OCD)/CDER/FDA

January 14, 2020
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NDA 211802 - Oxycodegol

Components of Abuse Potential Assessment for Discussion:

- Preclinical Pharmacology
- Clinical Pharmacology - Metabolism
- Two Oral Human Abuse Potential Studies
- Adverse Events Related to Abuse Potential
- Clinical Withdrawal

Acronyms

Cmax = Maximum plasma concentration; Tmax = Time to Cmax; AUCt and AUCinf = Area under concentration versus time curve to last time point and extrapolated to infinity, respectively; Emax = Maximum effect; TEmax = Time to Emax; AEs = Adverse Events

Oxycodegol - Preclinical

- Results of preclinical pharmacology studies (in vitro and in vivo) are consistent with oxycodegol being a mu opioid agonist.

- In situ and in vivo studies in rats demonstrate that brain uptake of oxycodegol is more than 70- and 25-times, respectively, slower than that of oxycodone, likely due to side chain PEGylation contributing to a lower brain-to-plasma ratio for oxycodegol.

- Oxycodegol undergoes extensive metabolism in animals resulting in formation of pharmacological active metabolites. Metabolic profile may differ from that of humans.

- Oxycodegol, at doses 30 and 50-fold higher than oxycodone, generalizes to oxycodone following intraperitoneal and oral delivery in rats, respectively.

- Intravenous Self-Administration Studies
  - Rat studies – Saline-like or weak reinforcing efficacy observed.
  - Squirrel Monkeys – Some reinforcement was noted.

Metabolism in Humans

- Oxycodegol is extensively metabolized.
  - N-demethylation
  - O-demethylation
  - O-dealkylation
  - Oxidation
  - Glucuronidation
  - Partial loss of the PEG chain.
  - Full loss of the PEG chain yielding 6-oxycodol
  - Oxidation of 6-oxycodol to produce oxycodone

- Twenty-seven metabolites of low abundance (each < 10% of total drug exposure) have been identified in plasma, urine, and feces of human subjects.

- Some of the metabolites have demonstrated low affinity binding at the human mu opioid receptor. A subset of these metabolites have demonstrated analgesic activity in animal models of analgesic activity.

Metabolites of Oxycodegol in Human Plasma

Mass Balance Study

(Single Oral 400 mg (100 µCi) of ^{14}C-Oxycodegol)

OH-PEG1-Oxycodol
OH-PEG2-Oxycodol
OH-PEG3-Oxycodol
OH-PEG4-Oxycodol
Carboxymethyl PEG1-oxycodol
Carboxymethyl PEG2-oxycodol
Carboxymethyl-PEG3-Oxycodol
Carboxymethyl PEG4-oxycodol
Carboxymethyl PEG1-Noroxycodol
Oxycodol-6-glucuronide
Carboxymethyl oxycodol
N-desmethyl-oxycodegol

- Oxycodegol in plasma constituted 49% of the total dose (radioactivity)
- Each metabolite constituted less than 10% of dose (range 9.2% to 0.4%)
- Collectively, metabolites constituted about 35% of the dose.
- Oxycodol and oxycodone were not documented.

Opioid Activity of Oxycodegol Metabolites

Inhibition of Radiolabeled Naloxone to the Human Mu Opioid Receptor.

Substance	Mean IC50 nM	Mean Ki nM
Oxycodone	71	50
6-Alpha-Oxycodol	950	670
6-Alpha-hydroxyPEG1-oxycodol	440	310
6-Alpha-hydroxyPEG2-oxycodol	400	280
6-Alpha-hydroxyPEG3-oxycodol	410	290
6-Alpha-hydroxyPEG4-oxycodol	420	300
6-Alpha-hydroxyPEG5-oxycodol	500	350
6-Alpha-hydroxyPEG6-oxycodol	530	380
6-Alpha-methyl carboxylic acid-oxycodol	670	480
6-Alpha-Oxycodol Glucuronide	1090	770
Des-Methyl-mPEG6-Oxycodol	2850	2020

Mouse Acetic Acid Writhing Test

Substance	Estimated ED50 mg/Kg, p.o.
Oxycodone	3
6-Alpha-Oxycodol	3
PEG-1-Oxycodol	3
PEG-2-Oxycodol	2
PEG-3-Oxycodol	20
PEG-4-Oxycodol	4
PEG-5-Oxycodol	30
Oxycodegol	7

Phase I Dose Escalating Studies

Oxycodone and Oxycodol as Metabolites

Phase 1 Clinical Studies	Oxycodegol Dose (mg)	Human Plasma Concentrations Following Oral Dosing					
		Oxycodegol (ng/mL)		Oxycodol (ng/mL)		Oxycodone (ng/mL)	
		Cmax	Tmax	Cmax	Tmax	Cmax	Tmax
Study 11-PXC-02	100	642	2.3	3.74	3.13	2.42	4.25
	200	1254	2.3	9.32	3.0	4.98	3.54
	300	2214	2.5	14.06	3.08	8.04	3.58
	400	3140	2.0	18.96	2.56	11.28	2.85
Study 14-181-10	400	2849	1.8	21.5	2.59	11.1	2.88
	600	4598	1.46	34.7	1.85	17.8	2.52
	800	6555	1.29	49.5	2.08	23.8	2.21
	1000	6574	1.54	54.7	2.17	26.2	2.45
	1200	7581	1.21	56.7	1.75	27.4	2.63

Oral HAP Study 12-181-05

- **Standard Design** - Single-center, randomized, double-blind, active and placebo-controlled five-period crossover study with Screening, Qualification, Treatment and Follow Up
- **Measures**: Drug Liking VAS, High VAS, Take Drug Again VAS, Overall Drug Liking VAS
- **Five Oral Treatments**:
  - Oxycodegol 100 mg, 200 mg, and 400 mg in oral solution
  - Oxycodone 40 mg in oral solution (comparator)
  - Placebo (Denatonium benzoate) solution

<u>Problems with study</u>.

- Supratherapeutic doses were not examined – Contrary to 2010 FDA Abuse Potential Guidance Document.
- Poor response of oxycodone 40 mg on Take Drug Again VAS and Overall Drug Liking VAS.
- No documented abuse-related adverse events associated with oxycodone 40 mg.
- Metabolites, particularly, oxycodone were not examined for in plasma.

Oral HAP Study 15-181-15

- Randomized, double-blind, double-dummy, single-dose, placebo- and active-controlled, 6-period crossover design with Screening, Qualification, Treatment and Follow Up
- Standard pharmacokinetic (PK) and (PD) measures.
- Maximum effect (Emax) of Bipolar Drug Liking was primary endpoint.
- Other Measures: High VAS, Take Drug Again VAS and Overall Drug Liking VAS

Oral Tablet Treatments (To-Be-Marketed Formulation):

- Kyvoda 400 mg (Therapeutic)
- Kyvoda 600 mg (Therapeutic)
- Kyvoda 1200 mg (Supratherapeutic)
- Oxycodone HCl 40 mg
- Oxycodone HCl 60 mg
- Placebo

Pharmacokinetics

Oral Treatment	Dose mg	PK Parameters in Plasma (Mean + (SD)) (N = 58 to 62 Subjects)								
		Oxycodegol			Oxycodol			Oxycodone		
		Cmax ng/mL	Tmax Hours	AUC 0-Inf	Cmax ng/mL	Tmax Hours	AUC 0-Inf	Cmax ng/mL	Tmax Hours	AUC 0-Inf
Kyvoda	400	3390 (1820)	2.75 (1.05)	17500 (5380)	21.4 (6.57)	3.77 (1.19)	200 (49.6)	10.8 (3.08)	4.13 (1.12)	116 (21)
	600	5390 (2390)	2.23 (0.95)	25100 (8210)	35.8 (10.7)	3.14 (0.95)	308 (78.9)	18.0 (4.06)	3.49 (1.00)	186 (33.3)
	1200	9220 (3190)	1.77 (0.75)	44600 (14100)	85.1 (27.3)	2.47 (1.04)	636 (147)	40.8 (11.0)	2.69 (1.05)	391 (73.0)
Oxycodone HCl	40	----	----	----	----	----	----	60.4 (22.0)	1.94 (1.29)	392 (91.2)
	60	----	----	----	----	----	----	89.1 (39.5)	1.70 (1.44)	578 (143)

Plasma Oxycodone

Oral Treatment	Dose mg	Oxycodone PK Parameters in Plasma (Mean + (SD)) (N = 58 to 62 Subjects)		
		Cmax ng/mL	Tmax Hours	AUC 0-Inf
Kyvoda	400	10.8 (3.08)	4.13 (1.12)	116 (21)
	600	18.0 (4.06)	3.49 (1.00)	186 (33.3)
	1200	40.8 (11.0)	2.69 (1.05)	391 (73.0)
Oxycodone HCl	40	60.4 (22.0)	1.94 (1.29)	392 (91.2)
	60	89.1 (39.5)	1.70 (1.44)	578 (143)

Bioavailability Analyses Conducted by Clinical Pharm:

1200 mg Kyvoda relative to oxycodone 40 mg
- Cmax: 70% or ~ 28 mg oxycodone
- AUC0-inf: Equivalent to oxycodone 40 mg.

600 mg Kyvoda relative to oxycodone 40 mg
- Cmax: 31% or ~ 12.4 mg oxycodone
- AUC0-inf: 48% or ~19.3 mg oxycodone

400 mg Kyvoda relative to oxycodone 40 mg
- Cmax: 18% or ~ 7.3 mg oxycodone
- AUC0-inf: 30% or ~12 mg oxycodone

Oral HAP Study 15-181-15
Subjective Measures – 0-100 VAS

"At-the-Moment" Subjective Measures – Repeated out to 24 hours

- **Bipolar Drug Liking VAS**
  - Statement: *"At the moment my liking for this drug is"*
  - Anchors: 0 = Strong Disliking, 50 = Neither Like nor Dislike, and 100 = Strong Liking.
- **Unipolar High VAS**
  - Statement: *"At this moment, I am feeling high"*
  - Anchors: 0 = Not at All and 100 = Extremely.

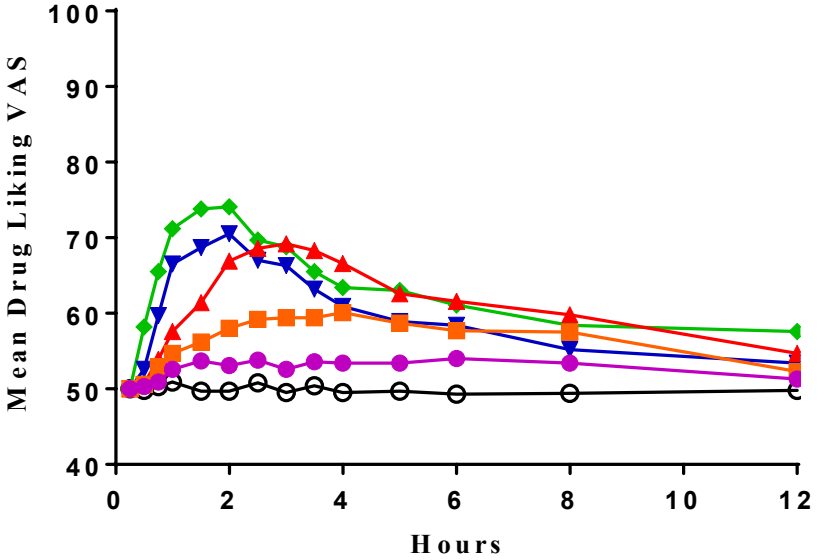
Global Subjective Measures – Take ONLY at 12 and 24 hours, post-dosing - Reflective

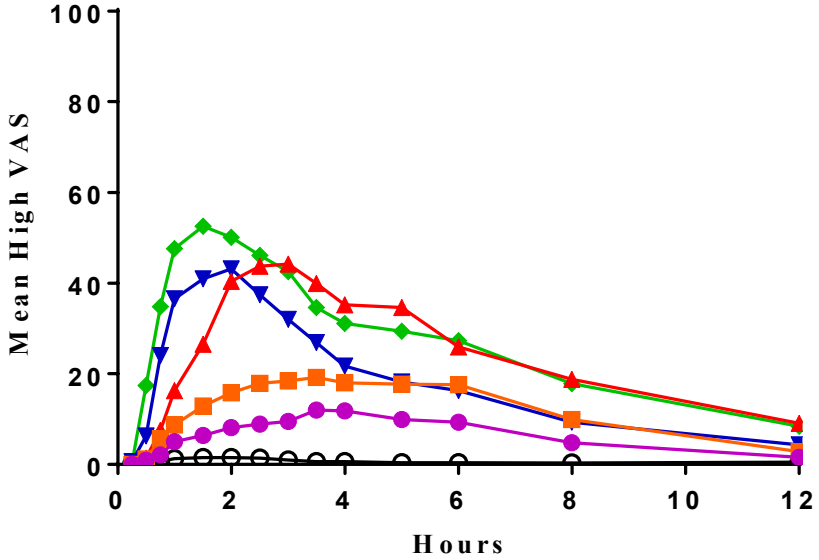
- **Bipolar Take Drug Again VAS**
  - Statement: *"Overall, I would take this drug again"*
  - Anchors: 0 = Definitely Would Not, 50 = Don't Care Either Way, 100 = Definitely Would.
- **Bipolar Overall Drug Liking**
  - Statement: *"Overall, my liking for this drug is"*
  - Anchors: 0 = Strong Disliking, 50 = Neither Like nor Dislike, and 100 = Strong Liking.

Oral HAP Study 15-181-15

"At-the-Moment" Drug Liking VAS and High VAS

Rate of rise for Drug Liking and High is slower for 1200 mg Kyvoda compared to 40 mg or 60 mg Oxycodone HCl IR.





Purple Circles 400 mg Kyvoda, **Orange Squares** – 600 mg Kyvoda, **Red Up-Triangles** – 1200 mg Kyvoda, **Blue Down-Triangles** – 40 mg Oxycodone HCl, **Green Diamonds** – 60 mg Oxycodone HCl

Study 15-181-15

"At-the-Moment" Subjective Measures

Subjective Measure	Mean ± SD Emax					
	Kyvoda 400 mg	Kyvoda 600 mg	Kyvoda 1200 mg	Oxycodone 40 mg	Oxycodone 60 mg	Placebo
Bipolar Drug Liking	61.6 ±13.2	67.4 ± 14.0	77.0 ± 13.1	76.8 ± 11.3	81.9 ± 13.1	52.3 ± 5.6
Unipolar High	20.7 24.7	33.1 ± 30.2	57.8 ± 25.6	53.8 ± 24.8	67.2 ± 24.3	3.0 ± 8.1

Mean Drug Liking TEmax (Hrs): NKTR 1200, 3.35; Oxy HCL 40 mg, 3.10; Oxy 60 mg: 2.63

Statistical Analyses

- No difference in mean Emax values of Drug Liking or High between Kyvoda 1200 mg and Oxycodone 40 mg.
- Oxycodone 60 mg, compared to Kyvoda 1200 mg, produced a higher mean Emax for Drug Liking. However the clinical relevance of the 5.1 points difference is not known.
- Kyvoda 400 mg and 600 mg produced mean Emax values for Drug Liking and High different from that of placebo indicating an absolute abuse potential for these two doses.

Study 15-181-15

"Global" Subjective Measures

Subjective Measures	Mean (SD) Emax					
	Kyvoda 400 mg	Kyvoda 600 mg	Kyvoda 1200 mg	Oxycodone 40 mg	Oxycodone 60 mg	Placebo
Bipolar Take Drug Again	65.2 ± 17.0	66.7 ± 21.0	77.8 ± 16.6	79.9 ± 16.1	83.4 ± 15.6	50.1 ± 8.2
Bipolar Overall Drug Liking	64.6 ± 16.2	65.6 ± 20.1	77.1 ± 14.9	79.2 ± 14.9	81.2± 15.4	51.1± 4.3

Statistical Analyses

- Mean maximum Take Drug Again or Overall Drug Liking were not different between Kyvoda 1200 mg and Oxycodone 40 mg.

- Oxycodone 60 mg and Kyvoda 1200 mg produced similar maximum Overall Drug Liking. The 5.6 points difference for Take Drug Again, although statistically significant is of unknown clinical relevance.

- Kyvoda 400 mg and 600 mg compared to placebo was associated with higher Take Drug Again and Overall Drug Liking indication an absolute abuse potential for these two doses.

Study 15-181-15
Additional Comments

- While 40 mg Oxycodone compared to 1200 mg Kyvoda as associated with a greater rate of rise in Drug Liking, this did not translate to differences in maximum responses for global assessments of Take Drug Again VAS or Overall Drug Liking VAS.

- While oxycodone may be considered a "minor metabolite" based upon total drug exposure, it likely contributes significantly, but not completely, to the subjective effects observed following oral oxycodegol. Additional contributions may come from the accumulative of active "minor metabolites" as well as oxycodegol, itself.

- Overall findings from Study 15-181-15 demonstrate that oxycodegol (as Kyvoda) has an abuse potential similar to that of oxycodone via the oral route of administration.

Overall Conclusions from Preclinical, Phase 1, and HAP Studies

- Oxycodegol is a mu opioid agonist, demonstrating slowed entry into the brain of rodents.
- Oxycodegol undergoes extensive metabolism in both laboratory animals and in humans. Some metabolites bind with low affinity at the human mu opioid receptor and display analgesic activity in animals models of analgesia. While each metabolite constitutes less than 10% of the total oxycodegol dose, collectively these metabolites represents a higher percentage of the oxycodegol dose and may contribute to the pharmacological effects observed.
- Oral HAP study 15-181-15 demonstrates a high oral abuse potential for oxycodegol that is most likely mediated principally by oxycodone, but also possibly by other metabolites as well as oxycodegol itself.
- Currently, the abuse potential of oxycodegol by intravenous injection is not known but will be the subject of future examination.

Abuse-related Adverse Events

Single Dose Ascending Studies

10-PXC-01 and 14-181-10

Abuse-Related AEs	Oxycodegol Dose (mg) (No. of Subjects)									Total	Placebo
	10-80 (47)	160 (12)	320 (12)	400 (12)	500 (12)	600 (12)	800 (12)	1000 (12)	1200 (12)	(143) (%)	(36)
Somnolence	0	1	2	3	0	1	3	4	6	20(14)	2
Feeling Relaxed	0	0	2	1	1	2	2	3	0	11(7.7)	0
Euphoric Mood	0	0	2	0	3	1	1	3	1	11(7.7)	1
Feeling Abnormal	0	0	0	0	4	1	0	2	0	7(4.9)	0
Elevated Mood				1				1		2	0
Feeling Drunk									1	1	0
Feeling Jittery								1		1	0
Sedation									1	1	0

Abuse-related AEs

Phase 1 Ascending Multiple Dose Studies

(11-PXC-02, 14-181-11, and 17-181-20)

	Number of Subjects (%) Displaying Abuse-Related AEs				
	Oxycodegol Dose (bid)				Placebo (N=19)
	100 mg (N=12)	200 mg (N=44)	300 mg (N=44)	400 –500 mg (N=77)	
Somnolence	3 (25)	3 (6.8)	6 (13.6)	12 (15.6)	1 (5.3)
Euphoric Mood	0	0	1 (2.3)	3 (3.9)	0
Feeling of Relaxation	0	0	0	5 (6.5)	0
Energy Increased	0	0	0	1 (1.3)	0

Abuse-related AEs

HAP Study 15-181-15

Abuse-Related AEs Study 15-181-15	Number (%) of Abuse-Related AEs					
	Oxycodegol			Oxycodone		Placebo (N=61)
	400 mg (N=59)	600 mg (N=62)	1200 mg (N=62)	40 mg (N=60)	60 mg (N=62)	
Feeling Abnormal	2 (3.4)	4 (6.5)	0	0	0	0
Feeling of Relaxation	0	1 (1.6)	0	0	1 (1.6)	0
Somnolence	3 (5.1)	3 (4.8)	6 (9.7)	7 (11.7)	10 (16.1)	1 (1.6)
Euphoric Mood	10 (17)	17 (27.4)	31 (50)	33 (55)	29 (46.8)	2 (3.3)
Hypervigilance	1 (1.7)	3 (4.8)	0	2 (3.3)	0	0

Abuse Related AEs – Phase 2-3 studies

- Rates of abuse-related AEs (euphoric mood, sedation) were lower than in Phase 1 and HAP studies likely due to lower doses being used in Phase 2/3 studies (highest dose of 400 mg in 2 studies and 600 mg in 1 study).

- A smaller number of patients (6.1% at 500 mg; 4.7% at 600 mg) received the highest doses compared to the lower doses.

- Although the number of abuse-related AEs were low, some caused patients to withdraw from the study (5 subjects with sedation and 2 with euphoria).

Physical Dependence

- Physical dependence was assessed in clinical studies by the administration of two scales: Clinical Opiate Withdrawal Scale (COWS) and Subjective Opiate Withdrawal Scale (SOWS).

- In Study 14-181-07 COWS measures were taken at 1 week following randomization, and SOWS measures were taken daily for 14-days following randomization.

- Prior to randomization, all subjects were titrated to a stable dose of oxycodegol for 2 weeks. Those randomized to placebo had their oxycodegol dose stopped abruptly. For two weeks following randomization subjects were allowed to receive 5 mg hydrocodone/ 300 mg acetaminophen as rescue medication

Physical Dependence

- The Sponsor reports similar COWS and SOWS scores between oxycodegol and placebo arms.

- However, COWS data would not have adequately captured withdrawal because the assessment took place 7 days after randomization (after abruptly stopping the drug when randomized to placebo); and likely had missed the peak of withdrawal, which for a drug with a half-life of 14 hours may be expected to peak around day 2 to 4. In addition, considering that opioid rescue medication was allowed for the first two weeks upon randomization the absence of occurrence of withdrawal is questionable

- Regarding SOWS data, although in Study 14-181-07 SOWS data was collected daily after randomization, it is unknown the degree to which the intake of opioid rescue medication impacted the findings. Rescue medication was taken more often by placebo than oxycodegol treated subjects

Abuse, Misuse, and Diversion in Clinical Trials

- Incidence of aberrant drug behavior and intentional abuse and diversion was assessed according to the Misuse, Abuse, and Diversion Drug Event Reporting System (MADDERS) in the two Phase 3 studies (14-181-07, 14-181-08)

- In Study, 14-181-07, three events classified as Abuse were all drug accountability discrepancies, and involved subjects returning less medication than expected. Two subjects had events of possible Diversion. In Study 14-181-08, four events were categorized as Abuse.

- These data indicate that, in the context of this clinical trial, subjects rarely abused or diverted study drug. However, abuse-related AEs such as euphoria, predictive of abuse potential, did occur during clinical development. Subjects enrolled in these studies were excluded if they had a history of substance abuse and may not represent the general population. Similar lack of aberrant drug behavior and intentional abuse during a clinical trial is observed in other trials of Schedule II opioids.

Conclusions

- In oral human abuse potential Study 15-181-15, 1200 mg oxycodegol (as Kyvoda) produced maximum effects on Drug Liking, High, Take Drug Again and Overall Drug Liking similar to that produced by 40 mg Oxycodone HCl.

- In oral human abuse potential Study 15-181-15 euphoric mood occurred at a rate of 17%-50% in oxycodegol treated subjects. Euphoric mood occurred in 17% of subjects at therapeutic doses of oxycodegol. Rate of euphoric mood was similar (50%) for both 1200 mg oxycodegol and 40 mg oxycodone, and well above placebo (3.3%).

- Results from the clinical assessment of Physical dependence were inconclusive.

- The lack of aberrant drug behavior and intentional abuse during the clinical trials is similar (low) to that observed in other trials of Schedule II opioids.

- Oxycodegol is considered to have abuse potential similar to that of oxycodone by the oral route.


FDA
U.S. FOOD & DRUG
ADMINISTRATION

CLINICAL EFFICACY AND SAFETY DATA SUPPORTING OXYCODEGOL AND BENEFIT-RISK EVALUATION

FDA Presentation

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee (AADPAC) and the Drug Safety and Risk Management Advisory Committee (DSaRM)

January 14, 2020

Jennifer Nadel, MD

Medical Officer DAAP/OND/CDER

Outline

- Introduction
- Efficacy
  - Patient population
  - Dose range
- Safety
  - Exposure data
  - Summary of safety findings
  - Hepatic safety
- Benefit: Risk evaluation

Background

- **Indication:** Management of chronic low back pain in adult patients with pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate
- **Class:** New Molecular Entity (NME) opioid
  - Full mu-opioid receptor agonist. A six-unit polyethylene glycol (PEG) chain has been added to the molecule with the goal of slowing the movement across the blood brain barrier

Overview of Applicant's Clinical Program

- Total of 15 Clinical Studies
  - 12 Phase 1 studies
  - 1 Phase 2 study
    - Double-Blind, Placebo-Controlled (Study 04) in osteoarthritis (4 weeks)
  - 2 Phase 3 studies
    - 1 Double-Blind, Placebo-Controlled (12 weeks) (Study 07) in chronic low back pain (CLBP)
    - 1 Open-Label long-term safety study (52 weeks) (Study 08) in chronic pain

Pooling of Data

- Pool 1: data from controlled studies
  - Phase 2 in OA (Study 04) and Phase 3 in CLBP (Study 07)
- Pool 2: data from uncontrolled Phase 3 study (Study 08)
  - Some patients from Study 07 rolled over into this study/group

EFFICACY DISCUSSION

Enrolled Patient Population

- Chronic opioids are not first-line therapy for chronic low back pain
- Previous meetings with Applicant to discuss appropriate patient population and appropriate enrollment criteria

Enrolled Patient Population

- What we know:
  - Study entry criteria
  - Concomitant medications at time of enrollment
  - Prior nonpharmacologic therapies
- Still unknown:
  - Doses of concomitant medications at enrollment or why they were not sufficiently controlling pain
  - Prior failed pharmacologic therapies and why they failed

Medications Used at Screening

Number of Back Pain Medications	Number (%) of Patients
1	678 (57%)
2	298 (25%)
3	86 (7.2%)
> 3	21 (1.8%)

Source: Applicant's Response to Day 74 Letter Request for Information, Table 2, page 12

Summary of Analgesic Medications at Enrollment

- **NSAIDs:** ibuprofen (52.4% [568 patients]), naproxen (28.4% [308 patients]), meloxicam (6.9% [75 patients])
- **Analgesics**: paracetamol (22% [238 patients]), oxycodone-acetaminophen (3.9% [42 patients]), acetylsalicylic acid (3.3% [36 patients])
- **Muscle relaxants:** cyclobenzaprine (5.9% [64 patients]), methocarbamol (1.8% [20 patients]), tizanidine (1.4% [15 subjects])

Prior Nonpharmacologic Therapies

	Total (N = 1083)
Number of Subjects with Prior Nonpharmacologic Therapies for Chronic Low Back Pain	
Yes	148 (13.7%)
No	920 (84.9%)
Missing	15 (1.4%)
Physical therapy	69 (6.4%)
Electric Stimulation Therapy (TENS)	6 (0.6%)
Acupuncture	4 (0.4%)
Chiropractic	64 (5.9%)
Massage	11 (1.0%)
Other	57 (5.3%)

Source: Applicant's Response to FDA Mid-Cycle Meeting Dated 13 December 2018

Titrated Doses Study 07

Titrated Dose	Number of Patients (%)				
	NKTR-181 (N = 309)	Placebo (N= 301)	Total Randomized (N = 610)	Not Randomized (N = 579)	Total (N = 1189)
100 mg	7 (2.3)	8 (2.7)	15 (2.5)	120 (20.7)	135 (11.4)
200 mg	63 (20.4)	57 (18.9)	120 (19.7)	79 (13.6)	199 (16.7)
300 mg	86 (27.8)	72 (23.9)	158 (25.9)	73 (12.6)	231 (19.4)
400 mg	**153 (49.5%)**	**164 (54.5%)**	**317 (52.0%)**	**307 (53.0%)**	**624 (52.5)**

Source: Summary of Clinical Efficacy, Table 3, page 29

Study 08 Dose After Protocol Amendment

Number of Patients	100 mg	200 mg	300 mg	400 mg	500 mg	600 mg
301	34	61	73	83	25	25

- Some patients needed to titrate beyond 400 mg for efficacy

Source: Response to Request for Information dated 05 December 2019, Table 1, page 1

SAFETY DISCUSSION

Titrated Doses Long-Term Safety (Study 08)

	All	100 mg	200 mg	300 mg	400 mg	500* mg	600* mg
Patients Enrolled	638	65	133	154	217	39	30

Source: Summary of Clinical Efficacy page 64, table 24

*19 additional patients titrated to the higher doses. They were patients who were in the dose titration phase when the Amendment was made

Oxycodegol Dose in Study 08

- Overall, 30 patients in Study 08 titrated to 600 mg, the maximum dose
  - 9 (30%) patients discontinued early
- 39 patients in Study 08 titrated to 500 mg
  - 11 (28.2%) patients discontinued early
- Insufficient safety data for doses >400 mg

Summary of Safety Findings for the Clinical Studies

- 1 death in Study 07
  - No other deaths reported to any other study
- 11 SAEs on oxycodegol reported for Pool 1
- 37 SAEs on oxycodegol reported for Pool 2
- Adverse events appear typical of an opioid
- Possible hepatic safety signal

SAE- serious adverse event

Death

- Study 07
- 64 y/o man with hypertension, hypercholesterolemia, obesity
- Occurred during open-label titration phase (Day 6) oxycodegol 100 mg twice a day
- Slurred speech (per roommate) and found in asystole by EMS
- Investigator coded as a CVA and unrelated to oxycodegol

CVA- cerebrovascular accident

Hepatic Safety

- 1 patient met the biochemical criteria for Hy's law but was diagnosed with acute hepatitis B
- No cases considered to be SAEs by Applicant
- There were 17 (1.2%) discontinuations due to LFT elevations in the Phase 3 studies
- The Applicant reported that 9 patients with ALTs > 3 X upper limit of normal (ULN) (but not so severe to be discontinued) were dosed through the elevation

LFT- liver function test
ALT- alanine aminotransferase
ULN- upper limit of normal

Category	Open Label Oxycodegol (N=1484)
Alanine Aminotransferase	
n	1453
> 2 to <= 3 X ULN	14 (1.0%)
> 3 to <= 5 X ULN	9 (0.6%)
> 5 to <= 8 X ULN	5 (0.3%)
> 8 X ULN	1 (<0.1%)
Alkaline Phosphatase	
n	1172
> 2 to <= 3 X ULN	4 (0.3%)
Aspartate Aminotransferase	
n	1450
> 2 to <= 3 X ULN	14 (1.0%)
> 3 to <= 5 X ULN	8 (0.6%)
> 5 to <= 8 X ULN	1 (<0.1%)
> 8 X ULN	3 (0.2%)
Total Bilirubin	
n	1440
> 1 to <= 2 X ULN	30 (2.1%)
> 2 X ULN	0

Summarized from ISS
Table 95, page 154

Category	Oxycodegol (N=416)	Placebo (N=407)
Alanine Aminotransferase		
n	413	405
> 2 to <= 3 X ULN	3 (0.7%)	2 (0.5%)
> 3 to <= 5 X ULN	0	0
> 5 to <= 8 X ULN	0	0
> 8 X ULN	0	0
Aspartate Aminotransferase		
n	412	404
> 2 to <= 3 X ULN	1 (0.2%)	2 (0.5%)
> 3 to <= 5 X ULN	1 (0.2%)	1 (0.2%)
> 5 to <= 8 X ULN	0	0
> 8 X ULN	0	0
Total Bilirubin		
n	407	399
> 1 to <= 2 X ULN	7 (1.7%)	9 (2.3%)
> 2 X ULN	0	0

Summarized from ISS
Table 98, page 158

	Number (%) of Subjects				
	Oxycodegol 100mg (N=135)	Oxycodegol 200mg (N=199)	Oxycodegol 300mg (N=231)	Oxycodegol 400mg (N=624)	Oxycodegol Total (N=1189)
N with lab values	118	199	231	624	1172
Alanine Aminotransferase [ALT]					
>= 3 X ULN	0	4 (2.0%)	4 (1.7%)	4 (0.6%)	12 (1.0%)
>= 5 X ULN	0	1 (0.5%)	2 (0.9%)	2 (0.3%)	5 (0.4%)
>= 10 X ULN	0	0	0	1 (0.2%)	1 (<0.1%)
Aspartate Aminotransferase [AST]					
>= 3 X ULN	0	3 (1.5%)	3 (1.3%)	6 (1.0%)	12 (1.0%)
>= 5 X ULN	0	1 (0.5%)	1 (0.4%)	1 (0.2%)	3 (0.3%)
Alanine Aminotransferase [ALT] or Aspartate Aminotransferase [AST]					
>= 3 X ULN	0	4 (2.0%)	4 (1.7%)	7 (1.1%)	15 (1.3%)
>= 5 X ULN	0	1 (0.5%)	2 (0.9%)	2 (0.3%)	5 (0.4%)
>= 10 X ULN	0	0	0	1 (0.2%)	1 (<0.1%)

Source: Response to Request for Information dated 27 March 2019 page 7-8

Hepatic Safety Patient Discontinuations

- 19 patients in the Phase 3 studies were discontinued for ↑LFTs
  - LFTs quickly reversed after drug cessation when that information was available
- 1 patient (400 mg dose) had 7.78 X ULN ALT, 9.36 X ULN AST, and RUQ pain
- 1 patient (400 mg dose) had 13.54 X ULN ALT, 4.71 X ULN AST, and total bilirubin of 1.85 X ULN

Benefit Risk Implications in Intended Patient Population

Benefits/Realities

- Met primary efficacy endpoint
- Safety similar to other opioids
- Benefit for patient population that need doses up to 400 mg

Risks/Uncertainties

- Indicated patient population unclear
- Unknown efficacious dose range
- Lack of safety data at doses >400 mg
- Potential liver signal
- Similar oral abuse potential to other Schedule II opioids